Screening drug-induced arrhythmia [corrected] using human induced pluripotent stem cell-derived cardiomyocytes and low-impedance microelectrode arrays.

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Public Summary:
Drug development is hampered by the unexpected side effect of these drugs on heart function. In particular, many drugs have been either withdrawn from market due to toxicity to the heart or prevented from further clinical development due to evidence of toxicity on artificial cell lines developed for the intent of eliminating toxic drugs. These assays, however, are imperfect due to their lack of similarity to human heart muscle cells. We developed an assay using heart muscle cell generated from human induced pluripotent stem cells to look at the effects of a comprehensive panel of drugs on the beating rhythm and contraction of these human heart muscle cells. We saw that may of the drugs that are know to cause heart rhythm issues also exhibit such behavior in human heart muscle cells generated from induced pluripotent stem cells (iPSCs). Our assay was able to to predict correctly drugs that cause abnormal rhythm issues in patients and ones that are safe. We believe this assay using human iPSCs is sensitive, robust, and efficient to test for the effectiveness of the drugs that treat abnormal heart rhythm as well as for predicting the toxicities of drugs on patients.

Scientific Abstract:
BACKGROUND: Drug-induced arrhythmia is one of the most common causes of drug development failure and withdrawal from market. This study tested whether human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) combined with a low-impedance microelectrode array (MEA) system could improve on industry-standard preclinical cardiotoxicity screening methods, identify the effects of well-characterized drugs, and elucidate underlying risk factors for drug-induced arrhythmia. hiPSC-CMs may be advantageous over immortalized cell lines because they possess similar functional characteristics as primary human cardiomyocytes and can be generated in unlimited quantities. METHODS AND RESULTS: Pharmacological responses of beating embryoid bodies exposed to a comprehensive panel of drugs at 65 to 95 days postinduction were determined. Responses of hiPSC-CMs to drugs were qualitatively and quantitatively consistent with the reported drug effects in literature. Torsadogenic hERG blockers, such as sotalol and quinidine, produced statistically and physiologically significant effects, consistent with patch-clamp studies, on human embryonic stem cell-derived cardiomyocytes hESC-CMs. False-negative and false-positive hERG blockers were identified accurately. Consistent with published studies using animal models, early afterdepolarizations and ectopic beats were observed in 33% and 40% of embryoid bodies treated with sotalol and quinidine, respectively, compared with negligible early afterdepolarizations and ectopic beats in untreated controls. CONCLUSIONS: We found that drug-induced arrhythmias can be recapitulated in hiPSC-CMs and documented with low impedance MEA. Our data indicate that the MEA/hiPSC-CM assay is a sensitive, robust, and efficient platform for testing drug effectiveness and for arrhythmia screening. This system may hold great potential for reducing drug development costs and may provide significant advantages over current industry standard assays that use immortalized cell lines or animal models.